REMARKS

Applicant thanks the Examiner for the opportunity to discuss the Office Action of August 4, 2003 during the interview of November 18, 2003 between the Examiner, Applicant, and Applicant's undersigned representative. This *Amendment* incorporates the substance of that interview.

I. 35 USC § 102 - Denick

The Rejection

Claim 1 stands rejected under 35 U.S.C. 102(b) as being anticipated by US 4,711,774 to Denick, Jr. et al (Denick).

The Examiner states that Denick discloses compositions containing guaifenesin mixed with magnesium aluminum silicate until a homogeneous mixture is obtained and indicates that magnesium aluminum silicate is used as an adsorbate for guaifenesin. The Examiner urges that, although Denick does not call it binder, magnesium aluminum silicate reads on the instant binder because the term is broad and does define any specific compound and further states that Denick discloses that the composition is dried and milled to produce a free flowing particulate material having a particle size of about 100 microns. Instant claim states less than 30% particles have a size greater than 425 microns, which includes 0%-30% and concludes that the composition of Denick therefore anticipates instant composition of claim 1.

Applicant's Claimed Invention

Applicant's claim 1 has been amended to require that the claimed guaifenesin composition comprises from about 85 to about 97.5 percent by weight guaifenesin and comprises particles that comprise guaifenesin particles and a binder. Support for the

amendment is provided at page 5, lines 20-23 (particulate guaifenesin), page 3, lines 15-18 (particles comprising guaifenesin and binder formed by drying agglomerate of guaifenesin particles), and page 5, lines 4-6 of the present specification (about 85 to about 97.5 percent by weight guaifenesin).

Denick

Denick describes an adsorbate made by sorbing a solution of a medicament, such as guaifenesin, onto a complex magnesium aluminum silicate sorbent (see col. 1, line 42 to col. 2, line 8 of Denick) and that the disclosed adsorbate contains only those medicaments which have first been dissolved in a solvent, such as, for example, water, and then sorbed onto the sorbent.

Denick Does Not Anticipate Applicant's Amended Claim 1

Denick discloses mixing a medicament solution, such as an aqueous guaifenesin solution, with a complex magnesium aluminum silicate to form a homogeneous mass (see col. 4, lines 35-38 and Example 1 of Denick), but Denick does not disclose guaifenesin particles or particles that comprise guaifenesin particles and a binder, as required by Applicant's amended claim 1. Since the disclosure of Denick does not satisfy the limitations of Applicant's amended claim 1, the disclosure of Denick does not anticipate Applicant's amended claim 1.

For the reasons discussed above, Applicant submits that Applicant's claim 1, as amended, is not anticipated by the disclosure of Denick and therefore requests that the Examiner reconsider and withdraw the rejection of that claims under 35 USC 102(b) as being anticipated by Denick.

II. 35 USC § 103 - D nick

The Rejection

Claims 5-8 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Denick.

The Examiner states that Denick teaches a particulate composition comprising guaifenesin and magnesium aluminum silicate, teaches that the particle size of the composition, upon milling to a free flowing composition, is about 100 microns and suggests that the particulate size ranging from 10 to 150 microns is suitable for the invention i.e., to prepare a guaifenesin composition containing magnesium aluminum silicate as an adsorbate.

The Examiner acknowledges that Denick differs from the instant claims in the percentages of particle sizes, but urges that it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to choose and obtain a guaifenesin composition having claimed particle sizes, because Denick teaches that suitable particle sizes in the range of 10-150 microns are preferred for absorbing sufficient quantities of medicament solution to prepare an acceptable drug product.

The Examiner further acknowledges that Denick does not state the flow rate recited in claim 8, but urges that, since Denick teaches particles in the same size range as required by the claims, optimizing the flow rate to produce a free flowing particulate formulation, having the claimed flow rate would have been obvious for a skilled artisan at the time of the instant invention.

Applicant's Claim's 5-8

Claim 5 had set forth an incorrect particle size distribution for the guaifenesin particles of the guaifenesin composition and has been cancelled.

Applicant's claims 6-8 each further limit the composition of Applicant's claim 1.

Applicant's Claims 5-8 Patentably Distinguish Over Denick

As discussed above in Applicant's remarks regarding the rejection under 35 USC 102(b) as being anticipated by Denick, Applicant's claim 1 has been amended to require that the claimed guaifenesin composition comprises particles that comprise guaifenesin particles and binder. Applicant's claims 6-8, each of which further limit Applicant's amended claim 1, now therefore include a limitation requiring that Applicant's claimed guaifenesin composition comprise particles that comprise guaifenesin particles and binder. As discussed above, Denick does not disclose any composition that comprises guaifenesin particles, as required by Applicant's amended claim 1.

Applicant submits that the subject matter of Applicant's invention would not have obvious at the time of the invention was made to a person having ordinary skill in the art in view of the disclosure of Denick because Denick's disclosure of a mixture of a liquid solution of guaifenesin and magnesium alumina silicate particles for the purpose of sorbing the dissolved guaifenesin onto the magnesium alumina silicate particles would not have suggested Applicant's claimed particles that comprise guaifenesin particles and binder to such a person.

For the reasons discussed above, Applicant submits Applicant's claims 6-8 patentably distinguish over the disclosure of Denick and therefore request that the Examiner reconsider and withdraw the rejection of claims 6-8 under 35 U.S.C. 103(a) as being unpatentable over Denick.

III. 35 USC § 103 - Blum /Mors

The Rejection

Claims 1-10 and 30-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,372,252 (Blume) in view of U.S. 4,269,859 (Morse).

The Examiner states that Blume teaches sustained release formulations comprising guaifenesin, a hydrophilic polymer such as hydroxypropyl methylcellulose, a water soluble polymer and other tabletting ingredients such as lubricants, binders, glidants, stabilizers and other excipients, and that Blume teaches preparing the composition by granulation and compression, which includes as one of the steps, drying and milling the composition and passing through sieves of 100 mesh screen size. The Examiner further notes that a 100-mesh size screen allows for particles of 150-micron size and acknowledges that Blume does not teach the exact percentages of the particle sizes as claimed by Applicant.

The Examiner states that Morse teaches a method of tabletting using cellulosic floc granules, which acts as a binder and a disintegrant, and which imparts good flow and binding characteristics, that making tablets by direct compression involves three requisites: free-flowing particulate material, binding properties of the material and material that does not stick to punches or dies, that the cellulosic binding material should have an average particle size in the range of 20 and 55 microns or even 30 to 40 microns, and that the cellulosic particles of the above size range impart a good flow properties and adequate tablet hardness, binding strength and stability due to the flow rate and the binding properties for binding the tablet to itself

The Examiner states that Morse suggests admixing the cellulosic floc with other pharmaceutical excipients such as starch, lactose, dextrose, mannitol, carboxymethyl cellulose; lubricants such as magnesium stearate, PEG and other excipients such as talc, silica, dicalcium phosphate, and that the amount of excipients, lubricant or binder should

not be employed at such levels as to reduce the necessary and desirable free-flow characteristics of the cellulose granules themselves.

The Examiner concludes that it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to use the appropriate particle sizes binders, disintegrants and such tabletting aids in the guaifenesin containing composition of Blume because Morse teaches that free-flowing characteristics in a compressible table preparation is a function of particle size and that the free-flowing binder material with a particle size of 30 to 55 microns imparts the desired hardness, strength and stability to the tablet, and optimizing the amounts of binders, lubricants and other excipients in the guaifenesin comprising medicament formulation of Blume would have been within the scope of a skilled artisan because Morse suggests that the amounts of excipients should be such that the flow characteristics should not be affected.

Applicant's Claims 1-10 and 30-38

Applicant's claim 1 is discussed above. Claims 5 has been cancelled. Claims 2-4, 6-10, and 30 each further limit claim 1.

Claim 31 has been amended to require that the composition comprises from about 85 percent by weight to about 97.5 percent by weight guaifenesin and comprises particles that comprise guaifenesin particles and binder. Support for the amendment is provided at page 5, lines 20 23, page 3, lines 15-18 and page 5, lines 4-6 of the present specification.

Claim 32 has been cancelled.

Claims 37 and 38 have each been amended to require that the composition comprises particles that that comprise guaifenesin particles and binder. Support for the amendment is provided at page 5, lines 20 23 and page 3, lines 15-18 of the present specification.

Blume

Blume discloses a directly compressible guaifenesin granulation comprising 95% guaifenesin and 5% binder that is made by granulating, milling and screening a mixture of guaifenesin and a binder (see col. 7, line 63 to col. 8, line 43 of Blume). As acknowledged by the Examiner, Blume does not disclose a guaifenesin composition having the particle size distribution required by Applicant's claims. Blume discloses that "not more than about 30% of the resulting granulation comes through a 100 mesh screen and that not more than about 10% of the resulting granulation is retained on a 10 mesh screen" (see col. 8, lines 19-23 of Blume), that is, at least 60% of Blume's granulation has a particle size of greater than 150 micrometers (the size of the openings in a 100 mesh screen) and less than 200 micrometers (the size of the openings in a 10 mesh screen).

Morse

Morse does not disclose a guaifenesin composition having the particle size distribution claimed by Applicant. Morse is directed to cellulose granules having a particle size distribution wherein less than 5% of the cellulose granules are retained on a 35 mesh screen, less than 30% of the cellulose granules are retained on a 100 mesh screen and less than 5% of the cellulose granules are retained on a 200 mesh screen and that comprise cellulose fibers having an average length on their longest dimension of from 20 to 50 μm (col. 6, lines 4-23 of Morse).

Morse recognizes that flow rate of a particulate mixture that comprises Morse's cellulose granules is impacted by the respective identities of the various components of such mixture and the relative amounts of such components, as well as by the particle size distribution of the mixture. Morse discloses that such cellulose granules are free flowing, that "in some cases" the cellulose granules may be advantageously admixed with pharmaceutical excipients and/or binders (see col. 8, lines 45-49 of Morse), but that such pharmaceutical excipients, adjuvant or binders should not be employed at such

levels as to reduce the desirable free flow characteristics of the cellulose granules (see col. 9, lines 5-12 of Morse). Morse further cautions that this percentage admixture must be carefully considered because some commonly accepted excipients diminish the flow rate of the cellulose granules (col. 9, lines 5-18 of Morse).

Morse's experimental results indicate that the flow properties of mixtures of Morse's cellulose granules with other materials are unpredictable. The potentially dramatic impact of the identities and relative amounts of the other components of such mixtures on the flow rates of such mixtures is demonstrated in Samples 6-8 in Table II of Morse and in Example 14 of Morse, that is, in Sample 7 and in Example 14, mixtures of Morse's cellulose particles and microcrystalline cellulose did not flow at all under the conditions investigated.

Applicant's Claimed Invention Patentably Distinguishes Over Blume and Morse

The Examiner urges that it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to use the appropriate particle sized binders, disintegrants and such tabletting aids of Morse in the guaifenesin-containing composition of Blume, because Morse suggests that the amounts of excipients should be such that the flow characteristics should not be affected.

Applicant submits that a person skilled in the art would not have found it obvious to use the tabletting aids of Morse in the composition of Blume in a manner that would satisfy the requirements of Applicant's claimed invention, because such use is beyond the scope of the disclosure of Morse and Morse does not provide motivation for extrapolating beyond such scope. The results of Morse's working examples demonstrate that the flow rate of a mixture of Morse's cellulose granules and another material is unpredictable and must be determined empirically. The disclosures of Morse and Blume, particularly in view of the non-flowable particulate mixtures disclosed by Morse, could not have supported a reasonable expectation that use the tabletting aids of Morse in the composition of Blume would result in a flowable particulate mixture. The disclosures of

Morse and Blume may, at most, have merely rendered Examiner's proposed use of the tabletting aids of Morse in the composition of Blume obvious to try.

The Examiner's has urged that Morse's discloses that the flow rate of a mixture is a function of the particle size of the mixture. Applicant submits that Morse further discloses that such flow rate is also a function of the relative composition of such mixture. As discussed above:

- Morse recognizes that mixing Morse's cellulose granules with other materials will have an impact on the flow properties of such a mixture and cautions that proposed admixtures of cellulose granules with other materials must be carefully considered from the perspective of avoiding potential detrimental effect on flow rate, and

- Morse's experimental results clearly demonstrate that the effects of other such materials on flow rate of such a mixture are unpredictable and must be empirically determined.

Morse provides no guidance that would have allowed a person of ordinary skill to effectively apply the disclosure of Morse to the guaifenesin composition of Blume within the range of guaifenesin content now required by Applicant's amended claims. Morse provides no data or guidance of any kind regarding the flow properties of any mixture of cellulose granules or other tabletting aid with guaifenesin particles and provides no data or regarding the flow properties of any flowable mixture that comprises Morse's cellulose granules and greater than 50% of any other material. A person skilled in the art might, at most, have found it obvious to try to, for example, substitute the cellulose granules of Morse for the binder in Blume's mixture of 95% guaifenesin and 5% binder. However, Morse and Blume provide no suggestion or guidance that would have would have led a person skilled in the art to, with any reasonable expectation of obtaining a flowable particulate mixture, extrapolate the disclosure of Morse beyond the mixtures investigated

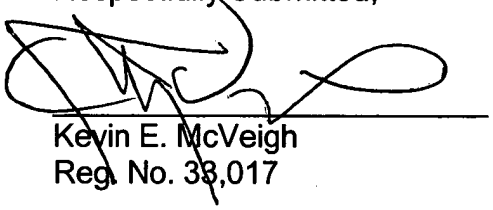
by Morse in order to modify the composition of Blume in a manner consistent with the guaifenesin content and particle size requirements of Applicant's amended claims.

For the reasons discussed above, Applicant submits that the subject matter of Applicant's amended claims would not have obvious at the time of the invention was made to a person having ordinary skill in the art in view of the disclosure of Morse and Blume and therefore requests that the Examiner now reconsider and withdraw the rejection of claims 1-4, 6 -10, 30, 31 and 33-38 under 35 U.S.C. 103(a) as being unpatentable over Blume in view of Morse.

IV. Conclusion and Request for Allowance

For all the reasons discussed above, Applicant submits that all claimed pending in the present application are in condition for allowance and now requests that the Examiner issue a *Notice of Allowance* for claims 1-4, 6-10, 30, 31 and 33-38 in the present Application.

Respectfully Submitted,



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